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(54) THERAPEUTIC AGENT FOR CORNEAL DISEASE

(57)Abstract:
PROBLEM TO BE SOLVED: To obtain a therapeutic agent capable of being used for the therapy of corneal damage such as the damage or the like of corneal epidermis, exemplified by corneal ulcer, and useful as an eye drop by making the agent include a ciliary nerve trophic factor as an active ingredient.
SOLUTION: This therapeutic agent contains a ciliary nerve trophic factor(CNTF) as an active ingredient. The CNTF can be produced by extracting human glia cell, and mass-produced according to a general gene recombinant technique. A buffer solution of boric acid or the like is used besides a sterilized purified water as the aqueous solvent used for the therapeutic agent, and an enhancer such as sodium chloride, a chelate agent such as sodium edetate, etc., are added thereto. The concentration of the CNTF in the objective therapeutic agent is preferably about 50 ng/ml to 2 mg/ml. The dose is preferably one to six drops (50 μl/drop) per dose, and one to five doses are preferably administered per day.

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Translation:

DETAILED DESCRIPTION

[Detailed Description of the Invention]

[0001]
[Field of the Invention] This invention relates to the ophthalmic remedy used for the therapy of the cornea breakages on epithelium-anterius-corneae failures including a corneal ulcer etc.

[0002]
[Description of the Prior Art] Cornea diseases including a corneal ulcer cause [of a visual field] reduction, or cause loss of eyesight. Moreover, infection of the herpes simplex (Herpes simplex) may cause a stubborn deficit of this epithelium anterius corneae. In addition, also by infection by bacteria or mold, a corneal ulcer happens and the cause by the activity of a contact lens is also said [many]. Moreover, it may go on for the disease of the nervous corneal ulcer (neurotrophic corneal ulcer) which loses some neurological functions.

[0003] Recovery of a cornea disease is said to little (late) flume crack and it that the viability (viability) and the metabolic turnover of the epithelium anterius corneae are involving according to breakage and denervation of a cornea nerve. The role to the nerve factor receptor of the flume crack which cutting of the trigeminal nerve in an animal decreases [crack] the amount of neurotransmitter acetylcholine, and decreases the cell division rate of a cornea epithelial cell, and this cornea epithelial cell is expected. One of them is a nerve growth factor (NGF), and it is an epidermal growth factor (EGF), a fibroblast growth factor (FGF), etc.

[0004] And to the abnormalities of an epithelium-anterius-corneae failure or a precorneal tear film, NGF, hyaluronate sodium, EGF, etc. are tried (a Japanese eye meeting magazine, 88 volume 9 No. 55 (Showa 59)), and it is reported in the clinical trial for a corneal ulcer that NGF obtains the outstanding curative effect (N.Engl.J.Med.338(17) and 1174 (1998)). Moreover, it is thought that NGF promotes survival and growth of a cell with wide range non-nerve cell, for example, immune system cell, external secretion system cell, etc. (Science 237, 1154 (1987)).

[0005] However, it is reported that the effectiveness with strong EGF or FGF of an operation of cell division in the culture experiment of a cornea epithelial cell decisive in this clinical trial was not acquired (N.Engl.J.Med 338 (17) 1222 (1998)). Thus, although various nerve factors and growth factors are tried by the therapy of a cornea disease, the actual condition is being unable to predict what kind of factor being effective.

[0006]
[Problem(s) to be Solved by the Invention] Therefore, the object of this invention is to provide the therapy of a cornea disease with a useful new remedy.

[0007]
[Means for Solving the Problem] When this invention person inquired wholeheartedly in view of this actual condition, the ciliary nerve nutritional factor (Ciliary Neurotrophic Factor: call it Following CNTF) completed header this invention for a little and strong curative effect being shown to the cornea disease.

[0008] That is, this invention offers the cornea disease therapy agent which makes CNTF an active principle.

[0009]
[Embodiment of the Invention] the existence gets to know CNTF as a ciliary nerve nutritional factor -- having -- other nerve growth factors (NGF), a brain-derived neurotrophic factor (BDNG), and neuro -- fatty tuna -- it is one of the neurotrophic factors in a fin (NT), a neuroglia origin neurotrophic factor (GDNF), etc.

[0010] The effectiveness over the disease of the motor neuron to which there are some applications to the medical care of CNTF, and CNTF exists in the central nerves (JP,5-199879,A), The breakage on the retina by the specific factor, and prevention of denaturation (Patent Publication Heisei No. 507053 [seven to]), The therapy approach (Patent Publication Heisei No. 503195 [ten to]) of bleeding disorder, glaucoma, the disease of an ophthalmic nerve, There is a report of neuropathy treatment (WO98432448) with the treatment approach (WO9719694) of the treatment (WO9832448) of encephalopathy, the therapy (WO9810785) of the glaucoma by ophthalmic solutions, retina nerve damage, and denaturation and ****** etc. However, there is no report of the purport which can use these reports for the therapy of a cornea disease based on the idea of being a factor with indispensable CNTF at nervous survival.

[0011] Although CNTF is producible by extracting from a Homo sapiens neuroglia, since Homo sapiens's CNTF gene sequence is already determined (EMBL DataLibrary:x60542), it can mass-produce according to general gene modification technology, and the stability of the gene recombination mold CNTF is also comparatively good.

[0012] Since CNTF calls it the matter in the living body, it is comparatively considered to be insurance, and in the Homo sapiens clinical trial (ALS:Amyotrophic Lateral Sclerosis amyotrophic lateralsclerosis), by hypodermic administration of rhCNTF, if it is below 5microg/kg / day, the report it is supposed that the side effect did not appear is made (1331 Neurology 47:1329- 1996).

[0013] As shown in the after-mentioned example, CNTF showed the powerful curative effect in a minute amount called 5 ng/mlCNTF to the cornea blemish model which used ******. This to CNTF is useful for the therapy of various cornea diseases, for example, a corneal ulcer, dry eye, a punctiform surface karatopathy, a simplicity epithelium deficit, a prolongment nature epithelium-anterius-corneae deficit, a recurrence nature epithelium-anterius-corneae sore, etc.

[0014] The cornea disease therapy agent of this invention is an ophthalmic remedy, and using especially as ophthalmic solutions is desirable. As ophthalmic solutions, although oily ophthalmic solutions besides water-soluble ophthalmic solutions, suspensibility ophthalmic solutions, and milkiness ophthalmic solutions are illustrated, you may be which pharmaceutical form.

[0015] this invention therapy agent can be manufactured with a conventional method. As an aquosity solvent used by this invention, the buffer solutions, such as a boric acid besides sterile purified water, a phosphoric acid, an acetic acid, or a citric acid, are mentioned. In addition, antiseptics, such as chelating agents, such as various isotonizing agents, such as a sodium chloride, and disodium edetate, and a benzalkonium chloride, etc. may be added as occasion demands. As a solvent of oily ophthalmic solutions, a liquid paraffin, olive oil, etc. are mentioned and things usually used, such as methyl cellulose, hydroxypropylcellulose, hydroxypropyl methylcellulose or these salts, polyvinyl alcohol, and a polyvinyl pyrrolidone, are illustrated as a viscous agent. Moreover, as suspension, polysorbate 80, polyoxyethylene hydrogenated castor oil 60, and stearin acid polyoxy 40 grade are mentioned. Moreover, the component used for agents for ophthalmology other than this can be added if needed.

[0016] As for the CNTF concentration of the cornea disease therapy agent of this invention, it is desirable it to be desirable to carry out in 50 ng/ml - 2mg/ml, and to carry out in 75 ng(s)/ml - 1mg/ml especially, and, as for a dose, it is desirable to be 1-6 drops (one-drop 50microl), and to prescribe a medicine for the patient 1 to 5 times per day once.

[0017]
[Example] Although an example is given and this invention is hereafter explained further to a detail, this invention is not limited to these.

[0018] Punch cut the Millipore filter for example 1 sterilization in diameter of 6mm, and this was dipped in n-heptanol. After having this **(ed) the rabbit of one groups [six] at random, having carried out general anesthesia with pentobarbital sodium (40 mg/body i.v.), performing eye surface anesthesia by oxyprocaine further and opening a palpebra greatly using the eye speculum, the Millipore filter dipped in previous n-heptanol was put on the cornea. The after [1 minute] filter was removed, after a physiological salt solution washed the palpebra, eyewash was applied and 50micro of 1% fluorescein solutions 1 was dyed. The excessive fluorescein solution was flushed with a physiological salt solution. It is PBS in 20micro of solutions 1 which carried out thawing processing and obtained rhCNTF as CNTF content pharmaceutical preparation. What added 9.8ml, used as the CNTF2microg/ml solution, diluted this suitably further and was used as 40, 20, 10, and a 5 ng/ml solution was used. The isotonicity phosphoric-acid buffer (PBS) was used as control.

[0019] 100microeach 1 instillation of a CNTF solution or PBS was done at both eyes 3 times of 1 hour, 2 hours, and 3 hours [n-heptanol wound creation and] after.

[0020] In addition, in order to lessen lacrimation which affects the effectiveness of drugs as much as possible, one drop applied eyewash in atropine to five quotas of the wound creation by n-heptanol. A photograph is taken 24 hours after wound creation (photograph slit lamp SL-6E TOPCON CORP.), and it is dyeing area AREA-LINE It measured using METER (Super PLANIX beta and TATEYA Instrumentation system). It asked for recovery area from the difference of the dyeing area value after [the initial dyeing area value immediately after wound creation to] specimen processing, and it asked for the rate of recovery by the following formulas.

[0021]
[Equation 1]

[equation not included with machine-assisted translation]

[0022] A result is shown in a table 1.

[0023]
[A table 1]
[table not included with machine-assisted translation]

[0024] The administration group of 5ng, 10ng, 20ng, and 40ng is raising the rate of recovery intentionally to the rate of recovery of the control group 24 hours after wound creation being 48.68%. The test result in comparison with EGF is shown in a table 2 by the same approach.

[0025]
[A table 2]
[table not included with machine-assisted translation]

[0026] CNTF showed the almost same rate of recovery as EGF.
[0027] Ophthalmic solutions were prepared according to the formula of the example table 3 of manufacture.

[0028]
[A table 3]
[table not included with machine-assisted translation]

[0029] It prepared by carrying out formula 1 as following. A sodium dihydrogenphosphate and phosphoric-acid 1 hydrogen sodium are measured, and, in addition to sterile purified water, a phosphoric-acid buffer is created. After adding benzal chloride KOUNIMU liquid 50 to this and adding disodium edetate and a sodium chloride further, CNTF is measured to accuracy and, in addition, it mixes. After preparing volume and pH to accuracy, sterilization filtration of this is carried out using a filter. Moreover, other formulas 2-5 were prepared according to this.

[0030]
[Effect of the Invention] Even if the cornea disease therapy agent of this invention is CNTF of a minute amount, it shows the outstanding cornea disease curative effect. Therefore, this therapy agent is useful for the therapy of a corneal ulcer, dry eye, a punctiform surface karatopathy, a simplicity epithelium deficit, a prolongment nature epithelium-anterius-corneae deficit, a recurrence nature epithelium-anterius-corneae sore, etc.

CLAIMS

[Claim(s)]

[Claim 1] The cornea disease therapy agent which makes a ciliary nerve nutritional factor an active principle.

[Claim 2] The cornea disease therapy agent according to claim 1 which is eye drops.

[Translation done.]